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REVIEW

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Individualized blood pressure targets during postcardiac arrest intensive care

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Purpose of review
To discuss recent findings relevant to optimizing blood pressure targets in adult, postcardiac arrest (PCA) patients and whether to tailor these based on specific patient, cardiac arrest or treatment characteristics.

Recent findings
Observational data suggest that mean arterial pressure (MAP) below 65–75 mmHg in PCA patients is associated with worse outcome. A higher MAP could be beneficial in patients with chronic hypertension who more frequently have a right shift of the cerebral autoregulation curve. Two recent randomized pilot trials compared lower and higher MAP targets during PCA care and found no significant effect on biomarkers of neurological injury. The haemodynamic interventions in those studies did not use any cerebral perfusion endpoints beyond a static MAP targets during ICU stay. Individualized, dynamic MAP targets based on assessments of cerebral perfusion and tailored to the specifics of the patient, cardiac arrest circumstances and treatment responses may be more conducive to improved outcomes. Pilot data suggest that near infrared spectroscopy monitoring may be used to determine the cerebral autoregulatory capacity and an optimal MAP, but this approach is yet to be tested in clinical trials.

Summary
Current evidence suggests targeting a MAP of at least 65–75 mmHg in PCA patients. Future studies should focus on whether certain patient groups could benefit from higher and dynamic MAP targets.

Keywords
acute myocardial infarction, blood pressure, cardiac arrest, cerebral oxygenation, cerebral perfusion pressure

INTRODUCTION

The cause of death in patients with return of spontaneous circulation (ROSC) after cardiac arrest and admitted to an ICU, is either neurological, cardiogenic or related to multiorgan failure. In a single-centre study from France about one third of patients died from circulatory shock and two thirds from hypoxic ischaemic brain injury (HIBI) [1]. Death from circulatory shock occurred in general during the first 3 days whereas death from neurological injury occurred between days 3 and 5 [1]. Nonetheless, various degrees of early circulatory failure with high lactate and need for vasopressors were key features in all patients who experienced poor outcome. An adequate mean arterial blood pressure (MAP) is paramount to maintain organ blood flow and hence oxygen delivery sufficient to meet oxygen demands in the brain, the heart and other organs. Importantly, optimal MAP goals may differ over time and between patients. In this review we discuss haemodynamic goals in postcardiac arrest (PCA) patients and whether MAP targets should be individualized to improve in particular cerebral blood flow (CBF) and as a corollary neurological outcome.

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KEY POINTS

- Observational data suggest that the lowest MAP target is around 65–75 mmHg.
- Targeting higher MAP have theoretical benefits but the evidence from two randomized pilot trials did not show any alleviation of biomarkers of neurological injury.
- Limited data exist on the optimal type of vasopressors and inotropes but noradrenaline appears to have many positive effects.
- The influence of MAP on cerebral blood flow is highly dependent on individual thresholds for cerebral autoregulation that are often right-shifted in PCA patients, mainly in hypertensive patients or patients using antihypertensive drugs before cardiac arrest.
- The optimal MAP to sustain cerebral perfusion may vary from patient to patient but thus far there are limited data on whether its timely identification in ICU may be used to improve patient-centred outcomes following cardiac arrest.

PATHOPHYSIOLOGY OF HYPOTENSION AND PERFUSION CHANGES

Hypotension in PCA patients is multifactorial reflecting changes in cardiac output (CO) [stroke volume (SV) and heart rate] and vascular conductance [2]. An inflammatory response is commonly seen which is related to hypoxia and systemic ischaemia-reperfusion following ROSC and results in vasodilatation and low systemic vascular resistance [3,4]. Cardiac index is often low mainly in patients with acute coronary syndromes as the initial cause of cardiac arrest. In addition, most patients receive continuous infusions of sedative agents to induce and tolerate target temperature management (TTM), for example propofol, which may decrease cardiac contractility and vascular resistance. Studies have not demonstrated a difference in MAP related to the specific temperature for TTM [5].

The complex cardiovascular compromise observed in PCA patients may furthermore involve disruption to ventriculoarterial coupling, impaired arterial elastance and changes to arterial augmentation [6]. These factors may have important implications for the propagation of the arterial pressure wave and its translation into propulsion of blood volume [7] and introduce uncertainty regarding how to best monitor invasive arterial pressure. These aspects of MAP targets remain sparsely studied despite recent progress in hypertension research, a common cardiovascular disease in PCA patients [8].

In most PCA patients the systemic haemodynamic compromise is most notable in the first 24–48 h after which it generally resolves [9]. The CBF follows a slightly different time course [10] and after an early but brief (20 min) postcardiac arrest hyperaemic response as a result of vasoparalysis, a period of hypoperfusion follows that may last up to 12 h and mainly reflects an uncoupling of metabolic vasoregulation. In the final phase up to 72 h after ROSC, CBF is typically restored to normal but may again demonstrate a hyperaemic response [11,12]. The latter has been associated with nonsurvival [11] and likely reflects persistent loss of cerebrovascular resistance. The influence of MAP on cerebral perfusion during these phases is obviously quite divergent and a static MAP target may lead to both hypoperfusion as well as hyperperfusion at different points in time.

BLOOD PRESSURE AND CEREBRAL CIRCULATION

Cerebral circulation in health is tightly controlled by multiple regulatory systems that ensure homeostatic CBF despite a variable MAP, generally referred to as cerebrovascular autoregulation (CVAR) [13]. Increased sympathetic tone in the large vessels to the brain, in particular the tortuous part of the internal carotid artery, lead to vasoconstriction and in addition both the blood arterial tension of oxygen (P_aO_2) and carbon dioxide (P_aCO_2) take part in vasoregulation that is also influenced by the general haemodynamic state, that is MAP and CO. The pial vessels of the neurovascular unit are sensitive to changes in P_aO_2, P_aCO_2, MAP and mediators of metabolic demand also when exposed via the cerebrospinal fluid and form the pivotal component of CVAR capacity. Although MAP often receives most attention in relation to CBF, the bony enclosure of the brain means that the intracranial pressure (ICP) acts as a Starling resistor which becomes important in circumstances with markedly elevated venous pressure; both increased ICP and heart failure with raised venous pressure in PCA patients may thus offset the impact of MAP changes. Recent studies have highlighted that the almost canonized paradigm of effective CVAR between a MAP of 50 and 150 is not correct [14]. The lower limit of autoregulation appears to be close to a MAP of 70 mmHg [15] with CVAR more effective for increasing than for decreasing MAP [16] which combined suggest a far more pressure-passive CBF than conventionally appreciated [13].

As HIBI is the main cause of morbidity and mortality in PCA patients it is not surprising that methods to monitor cerebral tissue oxygenation and the influence of MAP on CBF have attracted considerable interest. Many methods may be used to monitor CBF after cardiac arrest [17,18], for example

transcranial Doppler (TCD), MRI, Xenon computer tomography and near-infrared spectroscopy (NIRS), but only TCD and NIRS are available in the ICU with sufficient ease of operation. This review will focus on NIRS given its capacity for continuous monitoring at the bedside with minimal operator dependence [19,20] and with automated analyses for CVAR available [21] as well as the authors' own research experience.

Near infrared spectroscopy is a noninvasive method to estimate regional cerebral oxygen saturation (rSO_2), typically in the superficial parts of the frontal lobes encompassing the watershed area between the anterior and middle cerebral arteries. Although there are many determinants of rSO_2, the major influence in a short (minutes) time window is CBF. By analysing the linear correlation between changes in rSO_2 versus concurrent changes in MAP in the time domain, often referred to as tissue oxygenation index (TOx), a quantitative assessment of CVAR may be obtained. The more positive the correlation, the more passively rSO_2 and thus CBF, behaves during MAP changes whereas a TOx of zero or even a negative correlation indicates preserved CVAR capacity. The lowest and highest MAP for which the TOx transgresses from preserved to lost CVAR, in most studies at a threshold of TOx 0.3, indicate the upper and lower limits of autoregulation whereas the MAP associated with the least TOx value indicates the optimal MAP at which CVAR is most effective. The use of NIRS to calculate TOx and derived indices of CVAR has been applied in several pilot studies of PCA patients [22–24], comatose patients in ICU [19] and in healthy volunteers [25].

BLOOD PRESSURE AND PERFUSION OF THE HEART

Coronary blood flow occurs during diastole and hence the DBP and heart rate are of major importance [26]. Similar to the cerebral circulation, coronary flow is kept relatively constant over a wide range of blood pressures (BP) [26]. Even after successful revascularisation the resistance to blood flow may be increased as a result of vasospasm, formation of microthrombi and tissue oedema that shift the coronary autoregulation curve to the right [6]. By increasing DBP one may increase coronary blood flow which theoretically could salvage the areas adjacent to the infarcted myocardium. An association between higher DBP and improved outcome after cardiac arrest was reported in one study [27]. In this study of 171 PCA patients treated in the ICU, low DBP during the first 6 h after cardiac arrest was associated with outcome whereas SBP was not. Within the constraints of the study design, no conclusions regarding the possible mechanism(s) for improved outcome can be drawn.

MEAN ARTERIAL PRESSURE TARGETS

Immediate targets after return of spontaneous circulation

There is significant variability in MAP between patients very early after ROSC [28]. After ROSC there is high risk of re-arrest and therefore adequate cardiopulmonary monitoring is paramount: continuous ECG to identify recurring arrhythmias, noninvasive or preferably invasive BP and continuous capnography [29]. Many PCA patients are initially tachycardic and hypertensive, especially if adrenaline has been administered during cardiopulmonary resuscitation. Given the 5–10 min half-life of adrenaline one should initiate aggressive treatment to maintain BP before the effects of adrenaline has disappeared. Few studies have assessed the immediate BP targets after ROSC. One retrospective study indicated that failure to achieve physiologic targets recommended in Guidelines, including a SBP target of 120 mmHg, during the prehospital phase increased the risk of poor neurological outcome [28]. Similar observations have been made in PCA patients on arrival to hospital [30,31]. Means to achieve these BP targets include infusion of crystalloid solutions and the administration of noradrenaline.

General mean arterial pressure targets in the ICU

Assessment of CO in PCA patients during TTM is challenging as large thermal noise generated by cooling catheters tends to overrule the small thermal signal by the thermistor in the right ventricle. However, there is linear correlation between mixed venous oxygen saturation (SVO_2) as a surrogate for CO and rSO_2. The optimal MAP in PCA patients should preserve brain perfusion, taking in to account a potential right shift of the CVAR curve, without exposing the heart to excessive afterload that may impair SV, CO and cerebral perfusion. In an observational study by Ameloot *et al.* maximal rSO_2 was achieved with a MAP of 87 mmHg with higher MAP's resulting in reductions of CO and rSO_2. In the same study, an average MAP between 76 and 86 mmHg and average SVO_2 between 65 and 70% were associated with maximal odds for survival with good neurological outcome. Several other studies have investigated associations between increased MAP and improved survival and neurological outcome [30]. Laurikkala *et al.* studied the area under

various MAP thresholds and compared these between patients with good [cerebral performance category (CPC) 1–2] and poor (CPC 3–5) neurological outcome. In an analysis excluding the last 6 h before death in the ICU it appeared that there was a significant difference in time and magnitude (i.e. area) below a MAP of 70 mmHg, but not at higher levels [9]. Similar findings have been reported by Kilgannon *et al.* [31] who showed that a MAP above 70 mmHg during the first 6 h after ROSC was associated with better neurological outcome (CPC 1–2) and in a separate study a MAP more than 90 mmHg was associated with improved neurological outcome (modified Rankin Scale, mRS $\leq$ 3) [32▪]. In an observational study by Russo *et al.* [33] focusing on patients undergoing therapeutic hypothermia at 33 °C the optimal MAP appeared to be at least 75 mmHg. In contrast, Grand *et al.* [34▪] found no interactions between TTM and MAP and reported impaired cognitive function (mini-mental state score <27) in patients with higher MAP. On overview of conducted observational studies on MAP and outcome after out-of-hospital cardiac arrest (OHCA) are provided in Table 1.

RECENT RANDOMIZED STUDIES COMPARING LOWER AND HIGHER MEAN ARTERIAL PRESSURE

Recently, two trials have randomized PCA patients between a lower (MAP 65–75 mmHg) and a higher MAP target (MAP 80–100 mmHg) (Table 2). In both trials, interventions were started on ICU admission and lasted for 36 h. The COMACARE trial published in 2018 randomized 120 patients with OHCA and ventricular fibrillation [35▪▪]. The mean dose of noradrenaline required to achieve the assigned MAP targets were around 0.05 μg/kg/min in the lower group and 0.20 μg/kg/min in higher group. The study showed that targeting higher MAP was feasible and safe. However, the study failed to show any difference in rSO_2 or any difference in the level of neuron specific enolase as a surrogate marker of the magnitude of neurological injury.

In 2019, the NEUROPROTECT study was published. The NEUROPROTECT trial randomized 112 OHCA patients (including 35 patients with non-shockable rhythm) to either a standard group with a MAP target of 65–75 mmHg or a haemodynamic optimization group that included a higher MAP target (MAP 85–100 mmHg) as well as an optimization of the mixed venous saturation (SVO_2 65–75%) [36▪▪]. No difference in the extent of brain injury as measured with diffusion weighted MRI at day 5 was found between the two groups. In contrast with COMACARE, patients randomized to receive the

Table 1. Recently published observational studies on association between mean arterial blood pressure and outcome after cardiac arrest

Study	Included patients	Incidence of hypotension	Factors associated with the occurrence of hypotension	MAP target associated with outcome	Impact of vasopressor use on outcome	Factors associated with different MAP target	Comment
Grand *et al.*	657 OHCA patients treated with TTM at 33 or 36 °C	23 % had MAP < 70 mmHg	More common with ST-elevation AMI	No association between MAP and a biomarker of neurological injury	NA	Same effect regardless of TTM temperature	Large study sample with well validated biomarker as the endpoint
Laurikkala *et al.*	412 OHCA patients	A third of patients had a mean TW MAP less than 76 mmHg. 50 % of patients received vasopressors	NA	MAP < 70–75 mmHg	Increasing vasopressor dose was not associated with outcome	Slightly stronger association in patients treated with TH	Large study with very granular MAP data with long-term neurological data
Roberts *et al.*	269 OHCA and IHCA patients	41% had mean MAP less than 90 mmHg	More common in the elderly, patients with chronic heart failure, IHCA and with prolonged time to ROSC	MAP > 90 mmHg better than MAP 70–90 mmHg	No increase in poor outcome with increasing doses of vasopressors	Stronger association in patients with hypertension	In this substudy patients with MAP less than 70 mmHg were excluded
Russo *et al.*	122 OHCA patients treated with TTM at 33 °C			MAP > 75–80 mmHg associated with improved outcome	Association present despite the use of vasopressors	Stronger association in younger patients and in patients with shockable initial rhythm	Study included only TTM patients
Young *et al.*	188 OHCA and IHCA patients treated with TH at 33 °C	30–40% of patients MAP < 80 mmHg	NA	No association between MAP and outcome	No association between vasopressor use and outcome		Used hourly blood pressures both invasive and noninvasive

AMI, acute myocardial infarction; CHF, chronic heart failure; IHCA, in-hospital cardiac arrest; MAP, mean arterial pressure; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; TH, therapeutic hypothermia; TTM, target temperature management; TW, time weighted.

Table 2. Two recent randomized controlled trials on comparing high and low mean arterial pressure targets patients resuscitated from out-of-hospital cardiac arrest

Study	Intervention	Included patients	Intervention group mortality	Control group mortality	Intervention good neurological outcome	Control group good neurological outcome	Comment
Jakkula *et al.*	MAP 65–75 mmHg compared to MAP 80–100 mmHg	120 OHCA patients with ventricular fibrillation	30%	33%	68%	62%	Study did not include standard use of inotropes or cardiac output monitoring
Ameloot *et al.*	MAP 65–75 mmHg compared to early goal directed optimization including MAP of 80–100 mmHg	112 OHCA patients with all initial rhythms	60%	53%	40%	38%	Study showed some trends toward better outcome in the haemodynamic optimization groups but the main endpoint of neurological injury on MRI was negative

MAP, mean arterial pressure; OHCA, out-of-hospital cardiac arrest; TTM, target temperature management.

intervention in NEUROPROTECT did not show the typical drop of rSO_2 during the first 12-h of their ICU stay. We hypothesize that unopposed use of noradrenaline as in COMACARE may result in inappropriate increase of left ventricle afterload, reduction in SV and cerebral perfusion whereas the more frequent use of dobutamine in NEUROPROTECT (as guided by continuous SVO_2 monitoring) may have better preserved SV and cerebral perfusion.

While these two trials were not powered for patient-centred outcomes, rather than targeting a higher MAP for all patients it seems plausible that treatment should be individualized and directed towards subgroups for whom a higher MAP is needed. A post-hoc analysis of the COMACARE cohort to evaluate NIRS based indices of CVAR is currently in progress [37].

MEANS TO INDIVIDUALIZE MEAN ARTERIAL PRESSURE TARGETS

Using near-infrared spectroscopy

Pham *et al.* [22] studied 23 PCA patients and showed that perturbed CVAR was present in 78% of patients in the first 3 days in ICU. Although there were no differences in MAP or rSO_2 levels between survivors and nonsurvivors, TOx was an independent predictor of outcome and discriminated between survivors (all with favourable neurological outcome) and nonsurvivors with an area under the curve of 0.88 [95% confidence interval (CI) 0.75–0.90]. Ameloot *et al.* [23] studied 51 PCA patients and found disturbed CVAR in 35%, typically in patients with pre-cardiac arrest hypertension. The time spent under the individual optimal MAP for CVAR was independently associated with nonsurvival (odds ratio 0.97; 95% CI 0.96–0.99). Sekhon *et al.* [24] investigated 20 PCA patients and 15% of TOx measurements indicated absence of CVAR during a median patient monitoring period of 30 h. Significantly, the TOx increased with temperature and worsening CVAR associated with increased temperature was also reported in an observational study of 85 acutely comatose neurocritically ill patients [38]. Collectively, these studies in PCA patients demonstrated wide range of CVAR disturbances with the optimal MAP between 76 and 103 mmHg. It is thus conceivable that a static MAP target of 65–75 mmHg in PCA patients could be associated with cerebral hypoperfusion. Relying on static 'one-size fits all' NIRS rSO_2 values may not work as a post-hoc study of the COMACARE study failed to show any association between either the highest, lowest, mean or median NIRS rSO_2 values and neurological injury measured with biomarkers or neurological outcome [39].

Based on comorbidity

In the study by Ameloot *et al.* [23], the presence of chronic hypertension was associated with a right shift of the CVAR curve. The calculated optimal MAP was significantly higher in patients with chronic hypertension. The two randomized pilot studies comparing low and high MAP [35▪▪,36▪▪] did not find any interaction between neurological injury (MRI findings or biomarkers) based on the presence of chronic hypertension, although limited statistical power precludes any firm conclusions. In one retrospective study from the TTM study group, lower MAP was associated with decreased renal function [40]. In the NEUROPROTECT trial on the other hand higher MAP was associated with increased urinary output but no difference in creatinine [36▪▪].

Based on presence of acute myocardial infraction

In the NEUROPROTECT trial there was a significant difference in troponin levels favouring the higher MAP group [36▪▪]. In the COMACARE trial there was a trend towards lower troponin levels in the higher MAP group [35▪▪]. A pooled analysis of both trials (unpublished data) suggest that in a subgroup of patients with shock and acute myocardial infarction verified with angiography, troponin levels over time were significantly lower in the high-MAP patients. This may be related to improvements of DBP and coronary perfusion that offsets increased myocardial oxygen consumption by using higher doses of noradrenaline. Although the number of life threatening arrhythmias' were not different between patients randomized to low versus higher MAP targets, these findings at least show that using higher doses of noradrenaline to increase MAP is safe and feasible even in patients with an acute coronary syndrome immediately after successful revascularization.

Mean arterial pressure targets and target temperature management

In a sub-study of the TTM trial Bro-Jeppesen *et al.* [5] studied BP, cardiac function and vasopressor requirements in patients treated with TTM at either 33 or 36 °C. They found that TTM 33 °C was associated with bradycardia and a lower CO which could explain a reduced lactate clearance. There was no major difference in MAP levels between TTM groups but patients treated at 33 °C required slightly more vasopressor support. A MAP less than 65 mmHg was associated with increased mortality and poor neurological outcome independent of TTM at 33 or 36 °C.

Oxygen and carbon dioxide

Both P_aO_2 and P_aCO_2 influence CBF and the arterial oxygen content. Thus, it seems reasonable to assume that the effects of targeting different MAPs may be modified by the concomitant P_aO_2 and P_aCO_2. The COMACARE pilot trial, which is limited by sample size, did not however, demonstrate any interactions between MAP and P_aO_2 or P_aCO_2 [41].

CHOICE OF VASOPRESSOR IN POSTCARDIAC ARREST PATIENTS

No study to date has directly compared different vasopressors in PCA patients. Vasodilatation is one feature of the postcardiac arrest syndrome with a decrease in systemic vascular resistance. Large amounts of fluid may be needed in selected patients. Noradrenaline has many beneficial properties as it effectively increases MAP without causing severe tachycardia. In a study including patients with cardiogenic shock, noradrenaline was found to be superior to adrenaline given the severe tachycardia and aggravated shock observed with the latter [42▪▪]. Indeed, in both the COMACARE and NEUROPROTECT trials most patients were treated with noradrenaline and the haemodynamic profiles of patients appeared favourable, with increases in MAP without severe tachycardia or arrhythmias [36▪▪,39].

AREAS OF FUTURE RESEARCH

Although it seems promising to target a patient tailored optimal MAP by real-time bedside monitoring of CVAR based on correlations between rSO_2 and MAP, some important questions remain to be answered. First, in typical PCA patients, rSO_2 drops during the first 12 h of ICU stay. Although it seems paramount to start any haemodynamic intervention as early as possible during this critical time window, determination of patient tailored optimal MAP may take several hours. In addition, it has been hypothesized that patient tailored optimal MAP may be a dynamical parameter that changes continuously during this critical time frame depending on levels on vasopressor support (noradrenaline may by itself cause some cerebral vasoconstriction), sedation and arterial carbon dioxide. Future observational studies need to solve these issues before pilot trials targeting patients tailored optimal MAP's are ready for prime time. Factors that may influence the optimal MAP in OHCA patients are outlined in Fig. 1.

The current Guidelines on PCA care do not recommend any one strict MAP target [29]. Instead the recommendation is to titrate MAP to an

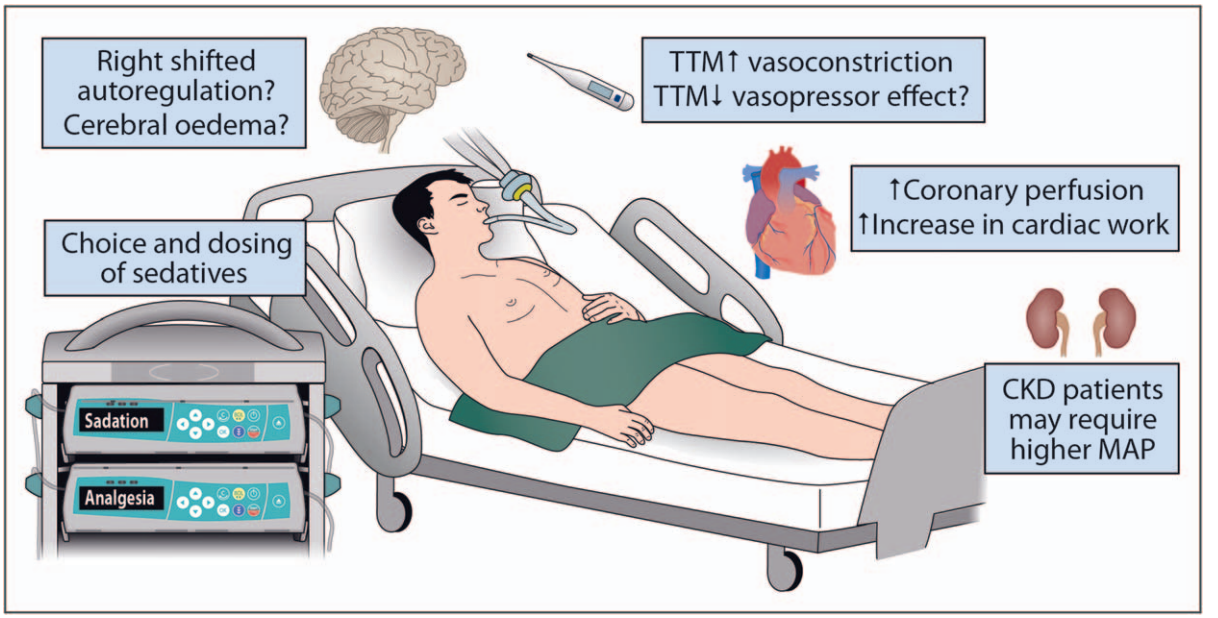

FIGURE 1. Comorbidities, pathophysiological and treatment factors that may influence the choice of minimal and optimal mean arterial pressure target in the cardiac arrest patient. CKD, Chronic kidney disease; MAP, Mean arterial pressure; TTM, Targeted temperature management.

adequate level in which lactate levels decrease and the patients has adequate urine output (0.5–1 ml/kg/h). Notwithstanding, a fairly large body of evidence suggest that it may not be wise to decrease MAP to levels below 70 mmHg. Future studies should focus on whether some subgroups of patients benefit from even higher MAP.

CONCLUSION

A MAP of 70 mmHg is likely to be adequate in most patients after cardiac arrest. Limited evidence suggest associations between better outcome and higher pressures in patients with an acute myocardial infarction, chronic hypertension and cerebral oedema. More refined ways to determine the optimal MAP requires further study before wider application.

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Conflicts of interest

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